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A Novel Role of CD38 and Oxytocin as Tandem Molecular Moderators of Human Social Behavior

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Highlights

- Oxytocin is an important modulator of human affiliative behaviors.
- This review discusses the social salience hypothesis of oxytocin action.
- Of special interest are studies of these two hormones in trust related behavior observed using behavioral economic games.
- The role of oxytocin in parenting and parental attachment.

Abstract

Oxytocin is an important modulator of human affiliative behaviors, including social skills, human pair bonding, and friendship. CD38 will be discussed as an immune marker and then in more detail the mechanisms of CD38 on releasing brain oxytocin. Mention is made of the paralogue of oxytocin, vasopressin, that has often overlapping and complementary functions with oxytocin on social behavior. Curiously, vasopressin does not require CD38 to be released from the brain. This review discusses the social salience hypothesis of oxytocin action, a novel view of how this molecule influences much of human social behaviors often in contradictory ways. The oxytocinergic-vasopressinergic systems are crucial modulators of broad aspects of human personality. Of special interest are studies of these two hormones in trust related behavior observed using behavioral economic games. This review also covers the role of oxytocin in parenting and parental attachment.
In conclusion, the effects of oxytocin on human behavior depend on the individual's social context and importantly as well, the individual's cultural milieu, viz. East and West.

Acronyms

ACC = Anterior Cingulate

ADP = Adenosine diphosphate

AQ = Autism Quotient

cADPR = Cyclic ADP-ribose

CNS = Central nervous system

DA = Dopamine

eQTLC= Expression Quantitative Trait Loci

LC-NE = Locus Coeruleus-Norepinephrine

MRI = Magnetic Resonance Imaging

OFC = Orbitofrontal cortices

OXT = Oxytocin

RAGE = Receptor for advanced glycation end-products

SARM1 = Sterile Alpha and toll/interleukin-1 receptor motif-containing 1

TRPM2= Transient Receptor Potential Cation Channel Subfamily M Member 2

AVP = Vasopressin

Keywords: oxytocin, CD38, CD157, human personality, social and affiliative behaviors, pair bonding

1. Introduction

Oxytocin is an important neuromodulator of human affiliative behaviors. Accumulating evidence from animal studies implicates the interaction of oxytocin and serotonin neurons in several aspects of social behaviour (Dölen et al., 2013; Lefevre et al., 2017; Pagani et al., 2015; Yoshida et al., 2009). Additionally, oxytocin-dopamine (DA) interactions have received considerable attention in mediating affiliative behaviors, again in preclinical studies (Charlet and Grinevich, 2017; Shahrokh et al., 2010). In this

review, CD38 as an immune marker and its mechanisms on releasing brain oxytocin are discussed. CD38, a transmembrane glycoprotein widely expressed in vertebrate cells, is a bifunctional ectoenzyme catalysing the synthesis and hydrolysis of cyclic ADP-ribose (cADPR). cADPR is a universal second messenger that releases calcium from intra- cellular stores. (Bartz and Hollander, 2006). *Altogether, interest in the mechanisms of action of oxytocin and CD38 is a major focus of the field of social neuroscience and the number of investigations in the past several years has grown considerably. Table 1 summarizes many of the recent studies in this area.*

2. CD38 as an immune marker

The history of CD38 initially focused on its role as an immune cell marker as detailed in a comprehensive review by Malavasi and his collaborators (Malavasi et al., 2008). At first, CD38 appeared to function solely as a marker for the investigation of thymocytes, activated T cells, and certain tissues. Additionally, in contrast with the idea that CD38 functions simply as an activation marker, end-stage differentiated plasma cells and their pathological corresponding cells showed the highest surface density among human cells (Quarona et al., 2013). A startling observation was the conspicuous similarity between human CD38 and the enzyme ADP ribosyl cyclase, initially purified from a mollusk – a phylum that predated the appearance of Homo *sapiens* by 700 million years. CD38 is an ectoenzyme, among many now known, found on the outside of the cell membrane. One important function of CD38 is a nucleotide-metabolizing ectoenzyme involved in the catabolism and recovering of extracellular nucleotides (Morabito et al., 2006). Since cADPR is generated by CD38 at the outer surface of

many cells, albeit it also acts intra-cellularly, and hence increasing attention is paid to addressing this topological paradox. It was demonstrated that CD38 is a catalytically active, unidirectional transmembrane transporter of cADPR, which then reaches its receptor-operated intracellular calcium stores (Zocchi et al., 1999). CD38 undergoes a selective and extensive internalization through non clathrin-coated endocytotic vesicles. A closely related paralogue of CD38 is CD157 apparently derived by duplication of the original CD38 gene (Ferrero et al., 1999). However, the role of CD38 as an immune cell marker and ectoenzyme is not the focus of review. Rather, we concentrate on the perspicacious observation by the Higashida group (Jin et al., 2007) who demonstrated that CD38 is critical for the release of central nervous system (CNS) and brain oxytocin (OXT). Since this initial discovery many review articles on this remarkable discovery have appeared (Deshpande et al., 2005; Feldman et al., 2016; Higashida et al., 2018, 2012; Lopatina et al., 2013; Meyer-Lindenberg et al., 2011; Morabito et al., 2006; Salmina et al., 2015, 2010; Shalev and Ebstein, 2013).

3. Mechanism of CD38 action on release of OXT (Chini and De Toledo, 2002)

Cyclic ADP-ribose (cADPR) was discovered in 1987 (Clapper et al., 1987). Successive studies showed that the Ca^{2+}release activity of NAD^+ was in fact due to conversion of NAD^+ to an active metabolite, later shown to be a cyclic compound derived from the ADP-ribose moiety of NAD^+ - cyclic ADPR (Lee et al., 1989). cADPR mobilizes Ca^{2+} by activation or sensitization of the so-called ryanodine receptor/channel (RyR) (Galione et al., 1991). Activation of CD38 by GTP-binding protein (G protein) and various types of receptors triggers formation of cADPR. cADPR opens Ca^{2+} release channels of ryanodine receptor type II or III (RyR) with another cofactor, Ca^{2}. Mobilization of

Ca^{2+} from microsomes of Ca^{2+} pools increases $[Ca^{2+}]_i$, resulting in OXT release In mammals ADP-ribosyl cyclase (CD38) is capable of generating both NAADP and cADPR (Aarhus et al., 1995). The unique Ca^{2+} releasing properties of NAADP suggests it is a candidate for an intracellular messenger. CD38 release of OXT is mediated by ryanodine receptor/channel and Ca^{2+} release of oxytocin in the brain. For example, increases in the intracellular free Ca^{2+} concentration in oxytocinergic hypothalamic cells are induced by cyclic ADP-ribose (cADPR), ADPR, and β-NAD+ sensitive to CD38 (Higashida et al., 2018). CD38 and Transient Receptor Potential Cation Channel Subfamily M Member 2 (TRPM2) are involved in triggering OXT release under physical (fever or heat) and chemical (NAD or cADPR) stimuli in both in vitro and in vivo conditions (Higashida et al., 2018).The scheme of how CD38 releases OXT is shown in the figure below (Fig.1) (Higashida, 2016).

4. Oxytocin and vasopressin

The mammalian oxytocin (OXT) and vasopressin (AVP) nonapeptides, named for their nine–amino acid structure, vary from each other at only two amino acid positions (Fig. 2). OXT and AVP are speculated to have emerged from a gene-duplication occurrence before vertebrate separation. Both nonapeptides vary by a single amino acid difference, and their genes are near each other on the same chromosome. Invertebrates mostly have only one oxytocin/vasopressin homolog, while vertebrates are characterized by two homologs (Acher et al., 1995).

~~In mammals, OXT and VAS are synthesized mainly in the hypothalamus and then ferried to the pituitary for either release into the peripheral target organs or alternatively~~

~~released to the amygdala and other brain regions.~~ Both OXT (OXTR) and AVP (AVPR1a and b) receptors show manifest variation in their brain expression profiles. OXT has one receptor, whereas AVP acts in the brain on its two centrally expressed receptor subtypes, V1a and V1b. AVPR1a functions more importantly in vasopressinergic modulation of social behavior and hence has been the focus of most research (Lim and Young, 2006). A review by Gimpl and Farenholz reported an excellent explanation of the oxytocin receptor system (Gimpl and Fahrenholz, 2001). The encoded OXTR receptor is a 389- amino acid polypeptide with 7 transmembrane domains and belongs to the class I G protein-coupled receptor (GPCR) (Gimpl and Fahrenholz, 2001). The gene is present in single copy in the human genome and was mapped to the gene locus 3p25–3p26.2. The gene spans 17 kb and contains 3 introns and 4 exons. Exons 1 and 2 correspond to the 5′-prime noncoding region (Zingg and Laporte, 2003). Exons 3 and 4 encode the amino acids of the OXTR. Intron 3, which is the largest at 12 kb, separates the coding region immediately after the putative transmembrane domain 6. Exon 4 contains the sequence encoding the seventh transmembrane domain, the COOH terminus, and the entire 3□-noncoding region, including the polyadenylation signals (Fig. 3).

5. The role of CD38 and OXT in human behavior

5.1. Social Salience hypothesis of OXT action on human social behavior (Shamay-Tsoory and Abu-Akel, 2016)

Tsoory and Abu-Akel (Shamay-Tsoory and Abu-Akel, 2016) , *following seminal work by Bartz and Hollander (Bartz and Hollander, 2006),* have suggested a novel theory of

OXT role in human social behavior that attempts to resolve some of the contradictory findings regarding this paramount human social hormone associated with prosocial and affiliative behaviour.

They argue that the effects of OXT on social behavior is primarily due to its tempering the salience of social cues in a situational-conditional way. Whereas OXT enhances trust, love and empathy to ingroup but not to outgroup members (De Dreu et al., 2010; Sheng et al., 2013), OXT may also evoke defensive systems of aggression with respect to outgroup members (De Dreu et al., 2010) as well as loved ones or close companions (DeWall et al., 2014), suggesting that OXT encourages aggressive leanings toward the "other" contingent on the type of the relationship between them. Such observations are compatible with investigations from animal research pointing to a role of OXT having an influence extending further than simple approach behavior. Interestingly, OXT (the so-called 'love hormone') also modulates selective aggression against male intruders in pair-bonded prairie voles (Young et al., 2008) and maternal aggression in postpartum and lactating rats (Leng et al., 2008). *Recently, a converging consensus has shown that intranasal oxytocin administration (INA) increases in-group preference and cooperation. Whilst there is some evidence for oxytocin increasing context-dependent aggression, such as protection to mates or offspring, more work is warranted to unambiguously demonstrate convincing support for the role of oxytocin in mediating increased aggression in humans (de Jong and Neumann, 2017). Moreover, accumulating evidence suggests that that the effects of INA oxytocin are negatively associated with aggression in animals and humans (de Jong and Neumann, 2017). A recent paper in humans showed a lessening in reactive aggression as revealed by*

examining rejection rates in the UG (Zhu et al., 2019). It should be noted, however, that the association between vasopressin and aggression in males is well established in both animal and humans studies (Berends et al., 2019; de Jong and Neumann, 2017). Shamay-Tsoory and Abu-Akel (Shamay-Tsoory and Abu-Akel, 2016) also suggest the notion that dopaminergic systems due to their role in attention are important in mediating the role of OXT and saliency in directing attention to the context in which OXT exerts its role in social behavior.

In contrast to the special function attributed to dopamine, through its interaction with Locus Coeruleus-Norepinephrine (LC-NE) system, OXT might play the key role in mediating the effects in attention orientin and hence social salience (Aston-Jones and Cohen, 2005).

There are many similarities between the LC-NE and DA systems. NE and DA are neuromodulatory neurotransmitters that have similar functional properties on their site of action systems (e.g., modulation of gain (Servan-Schreiber et al., 1990)); both are reactive to motivationally salient events (e.g., reward predictors); and dysfunctions of both have been caught up in overlapping groups of clinical disorders including schizophrenia, depression, and attention deficit disorder (Gradin et al., 2011; Kumar et al., 2008). Despite these similarities, the relationships between these systems and how they interact has remained unclear, in part due to the lack of formal theories about the function of either system. Montague et al. (1996) have proposed a sophisticated theory of DA function that suggests that it implements the learning signal associated with a reinforcement learning mechanism (Schultz et al., 1997). This theory affords a direct point of contact with the adaptive gain theory of LC-NE function. We argue that in many

respects the LC-NE system is complementary, if not an alternative, to the DA learning reinforcement system and that distinguishing between their actions on learning, attention and motivational behavior is a future challenge.

Oxytocinergic neurons that originate in the paraventricular nucleus (PVN) project to many important areas which integrate behavioral and cardiovascular reactions within the CNS. One of these areas is the major noradrenergic LC nucleus (Buijs, 1983). A large body of behavioral and electrophysiological studies suggests that the activity of the noradrenergic system emanating in the LC is correlated to alertness and attentiveness (Aston-Jones et al., 2007; Petersson et al., 1998). Thus, noradrenergic LC neurons regulate states of alertness and enhances the ability of the brain to react adaptively to environmental stimuli (Rajkowski et al., 1997). The results of the study by (Petersson et al., 1998), showing an increased responsiveness of LC alpha 2-adrenoreceptors following sub-chronic oxytocin treatment, indicate that LC-NE are likely involved in some of the important behavioral effects of OXT. There appears to be the need to consider the possibility of OXT acting as a moderator of social salience valence, as suggested by the novel theory by Shamay-Tsoory (Shamay-Tsoory and Abu-Akel, 2016), that it is mediated at least as much by the actions of this nonapeptide on the LC-NE system as its effect on the limbic dopaminergic systems.

5.2. Oxytocinergic-Vasopressinergic Systems and Personality

The oxytocin (OXT) system is one biological substrate that has been associated with individual differences in human behavior, social cognition and broad definitions of personality such as trust and generosity. There are studies showing that greater

concentrations of endogenous OXT is associated with higher trait novelty-seeking temperament (De Dreu et al., 2015) and secondly, OXT intra-nasal administration leads to increased holistic processing, more flexible thinking, more original ideas, and better creative problem solving (De Dreu et al., 2014). Intriguingly, Cardoso and colleagues (Cardoso et al., 2012) demonstrated that OXT administration is characterized by modifications in self-report personality. After intra-nasal OXT, subjects self-report higher Extraversion and Openness to Experience personality traits. These findings have driven the search for genes within the OXT system that confer individual differences in personality traits and social cognition.

In a recent study, Hass and his co-authors (Haas et al., 2018) explored the correlation between Big-5 personality traits (Costa and McCrae, 2008) and epigenetic modification of *OXTR*. They predicted that DNA methylation at the promoter region of the OXTR gene would be associated with individual differences in Openness to Experience. Furthermore, there currently exists a mixed pattern of results linking the OXTR gene with sociability (Bakermans-Kranenburg and Van Ijzendoorn, 2014). Hence, they explored the association between epigenetic modification of OXTR and prosocial personality traits, Extraversion and Agreeableness. To test their hypotheses, they conducted a multiple regression analysis with all Big-5 personality traits entered simultaneously as predictor variables and OXTR DNA methylation entered as the criterion variable (controlling for age and sex). The results indicate that Openness to Experience is associated with *OXTR* DNA methylation, while controlling for the remaining Big-5 personality dimensions (Neuroticism, Extraversion, Agreeableness, and Conscientiousness) and sex and age. This finding provides additional support for

models associating oxytocin with individual differences in personality and identity in humans.

5.3. Gratitude, Trust and trustworthiness

In an interesting paper (Algoe et al., 2014) implemented a genetic strategy to examine the hypothesis that social interactions involving expressed gratitude would likely be associated with SNP variations in CD38, which is crucial to brain release of OXT. The CD38 SNP (rs6449182), which is known to modulate CD38 expression, was significantly associated in laboratory and field experiments with global relationship satisfaction, perceived partner responsiveness and positive emotions (especially love), observed behavioral expression of gratitude toward a romantic partner in the lab, and frequency of expressed gratitude in daily life.

Trust in other people is a prerequisite of social affiliation and social bonding in humans. As an introduction to concept of trust and its importance in human relationships, we suggest the article by Van Lange (Van Lange, 2015) who fixes four basic lessons on trust: (a) Generalized trust is more a matter of culture than genetics; (b) trust is deeply rooted in social interaction experiences (going beyond childhood), networks, and media; (c) people have too little trust in other people in general; and (d) it is adaptive to regulate a “healthy dose” of generalized trust. Each of these lessons is inspired and illustrated by recent research from different scientific disciplines discussed in the article.

In Figure 4, the amount Y sent by Player 1 is referred to as Trust and the amount sent back by Player 2 out of 3Y is referred to as Trustworthiness. Kosfeld et al (Kosfeld et al., 2005) administered intranasal OXT to subjects and reported an increase in Trust in the

incentivized Trust Game, albeit no increase in Trustworthiness was observed. This seminal article has spawned a series of follow-up experiments in people using intranasal OXT as well as plasma OXT measurements to evaluate the role of this nonapeptide on social preference. In a subsequent study, Baumgartner and colleagues examined the effect of OXT on the neural circuitry underlying trusting behavior using fMRI (Baumgartner et al., 2008) and a modified trust game. The participants' initial trusting behavior was not reciprocated and intranasal OXT increases the tolerance to this lack of reciprocity compared with placebo. This difference in trust adaptation was associated with the attenuated activity of amygdala and midbrain regions (Baumgartner et al., 2008).

However, there is a caveat in the results first reported by Kosfeld and colleagues (Kosfeld et al., 2005). A more recent meta study by Nave et al (Nave et al., 2015) suggests that the association between intranasal OXT with higher trust has overall not been reproducible. Moreover, the measurements of plasma OXT in the Trust Game is plagued by controversy with both the reliability of measurement of plasma OXT (McCullough et al., 2013) and its relationship to brain levels of the hormone. In addition, genetic associations between the OXTR polymorphisms and Trust should be viewed in light of the small effect sizes of single polymorphisms and the difficulty in replicating such findings.

In summary, Nave et al (Nave et al., 2015) argue that the collective evidence does not generate robust convergent evidence that Trust is reliably associated or correlated with OXT. However, they do conclude their article with constructive ideas for improving the robustness and rigor of OXT research. Despite the critique of Nave et al, the association

between OXT and Trust continues to attract much attention, and continuing investigation in various fields, and hence despite the caveat, further research to better understood this important human personality trait seems warranted.

Indeed, there is considerable interest in the role of oxytocin in promoting interpersonal trust. However, as shown in a recent review and metanalysis by Nave and his colleagues (Nave et al., 2015) the role of oxytocin in promoting trust is apparently weak. Nave et al note that "Unfortunately, the simplest promising finding associating intranasal OT with higher trust has not replicated well. Moreover, the plasma OT evidence is flawed by how OT is measured in peripheral bodily fluids. Finally, in recent large-sample studies, researchers failed to find consistent associations of specific OT-related genetic polymorphisms and trust", Rather than an effect on trust, a recent paper suggests the intriguing notion that oxytocin is increasing conformity, specifically to the opinions or advice of the most trusted individuals and/or experts (Xu et al., 2019).

In an interesting article, Nishina and colleagues (Nishina et al., 2018) may have shed some light on possible reasons for the lack of robust evidence for a role of OXTR in Trust-related behaviors. Previous studies have shown that genetic variations in rs53576, a common variant of *OXTR*, are correlated with Trust in men (Nishina et al., 2015). Since the path from polymorphism to behavior is circuitous and difficult to unravel, Nishina and colleagues further examined whether amygdala volume mediates the association between *OXTR* rs53576 genotypes and attitudinal trust. Previously, Inoue and colleagues showed a correlation between the *OXTR* gene and amygdala volume in non-clinical subjects (Inoue et al., 2010). The rs2254298A allele of *OXTR* was

significantly correlated with larger bilateral amygdala volume and the A allele effect on amygdala volume was dose dependent. Two single nucleotide polymorphism haplotypes, including rs2254298G allele, showed significant associations with a decrease in bilateral amygdala volume.

Furthermore, Nishina and colleagues (Nishina et al., 2018) found evidence that left amygdala volume plays a pivotal role in the association between *OXTR* rs53576 genotypes and attitudinal trust in men. Unfortunately, it is difficult to establish convincing evidence for correlations between polymorphism x brain region x gender x behavioral trust as many unknown variables are contributing to these relationships.

Another interesting study from the Nishina and colleagues showed a relationship between *AVPR1a* (a paralogue of OXTR) and Trust (Nishina et al., 2019). Four-hundred and thirty-three participants played the Trust Game, answered the attitudinal trust question, and their buccal cells were collected. Results showed that men with a short form of *AVPR1*a tend to send more money to the opponent, even if there is a possibility of being betrayed by the opponent. Additionally, people with a short form of *AVPR1a* tended to return money to the opponent who trusts them. However, attitudinal trust was not associated with AVPR1a. These results indicate that arginine-vasopressin receptor 1a plays an important role in trust and reciprocal behaviors. Curiously, in a highly-cited study from our own group (Knafo et al., 2008) we showed that the long form of the *AVPR1a* RS3 allele is the prosocial allele and contributes to increased giving in the Dictator Game.

Another confound in establishing gene-behavioral correlations concerns individual emotional differences. For example, individuals high in social anxiety showed reduced

reciprocal, but intact trustful giving, pointing to a constraint in responsiveness (Anderl et al., 2018).

Another example of the complexity of Trust and genes is the recent study by Fang and co-authors (Fang et al., 2020). They note that long-term experience under stressful work environments can modulate an individual's general trust; not surprisingly, high job stress is associated with low trust in others perhaps suggesting a loss of executive control under such stressful conditions. It is difficult in simple gene association studies to consider many of the important demographic and environmental variables that are now known to temper many correlations between genes and behavior.

Both environmental and genetic factors contribute to general trust (Cesarini et al., 2008); however, few empirical studies have explored the important role of gene–environment interactions on general trust. In this study (Fang et al., 2020), the moderating roles of the polymorphisms *OXTR* rs53576 and *OXTR* rs2268490, job stress and general trust were evaluated in 362 Chinese Han university teachers (196 males, 165 females, and 1 undisclosed). Standardized questionnaires about demographic characteristics, job stress, and general trust scale were collected. Blood samples were collected for *OXTR* rs53576 and rs2268490 genotyping. The results showed that job stress scores showed a significant negative main effect on general trust ($p < 0.001$), while OXTR rs53576 and rs2268490 did not ($p > 0.05$). Nevertheless, there was a significant interaction between job stress and *OXTR* rs53576 or rs2268490 on general trust, controlling for gender and age. High job stress was correlated with low general trust in *OXTR* rs53576 homozygous individuals (GG/AA) or OXTR rs2268490 CT individuals, demonstrating that the GA genotype in *OXTR* rs53576 and CC/TT

genotype in *OXTR* rs2268490, which the authors suggest are therefore protective genotype of general trust.

Although there is an ever-increasing number of studies of OXT and human social behavior, due caution needs to be exercised in evaluating the role of this nonapeptide in shaping human behavior. In a recent review Zhao and colleagues have made some interesting points worth considering when evaluating the role of OXT in behavior (W. Zhao et al., 2019) and also see (Quintana and Woolley, 2016) as well as reply of Leng and Ludwig (Leng and Ludwig, 2016). Walum and colleagues have underscored the conundrum of low statistical power in many of the human studies (Walum et al., 2016) and Bartz and co-authors have emphasized the importance of 'context' when carrying out experiments with OXT (Bartz et al., 2011). Notably, replicability of findings of sniffing OXT have been questioned especially in connection with Trust (Nave et al., 2015) and see (Yao et al., 2014).

Yao et al (Yao et al., 2014) showed in a double-blind, between-subjects, placebo-controlled design study, two repair strategies (for restoring trust) were used to examine the effect of intra-nasal OXT administration on modulating trust restoration in a revised trust game. The results showed that although OXT had no overall effect on modulating trust restoration, it did have a significant gender specific effect. Female subjects showed less evidence for trust repair in the OXT compared with the placebo treatment group. This suggests that OXT may make female subjects exhibit more punitive behavior towards partners who violate their trust and less sensitive to repair strategies provided by them. Interestingly, this gender specific effect was more evident in the context of attempted trust repair using financial compensation. However, it also extended to

apology alone, and no compensation conditions, but not to the fair one, in females exhibiting high trait forgiveness. Thus, females with a more forgiving attitude towards betrayal may actually be more likely to punish betrayal following oxytocin treatment.

With respect to personal factors, converging evidence points to the important role of biological factors including sex (Feng et al., 2015a; Gao et al., 2016; Zhang et al., 2017; *Borland et al., 2019a, 2019b; Love et al., 2012; Luo et al., 2017)* and genetic variations, particularly individual differences in oxytocin-receptor gene (OXTR; located on chromosome 3p25) polymorphisms (Avinun and Knafo, 2013; Jones et al., 2017a; Kurian et al., 2011; Weisman et al., 2012; Wirth et al., 2015; Yang et al., 2010) among many.

Interestingly, some pharmaco-genetic studies examined how individual differences in *OXTR* genetics can impact the use of intra-nasal OXT. Modulatory effects have been reported in the domains of facial emotion recognition (Marsh et al., 2012) , social salience (Feng et al., 2015b; Jones et al., 2017b), and cooperation (Feng et al., 2015) suggesting that individual differences in OXTR genetics may account for the variable effects of intranasal OXT on interpersonal behavior.

5.4. Parenting: the role of OXT

5.4.1. Parental Attachment.

There are many studies showing greater influence of SNP variation of OXT-pathway genes with more caring parental behavior. Mothers characterized for the *OXTR* rs53576GG SNP were observed in more sensitive connections and communication with their babies (Bakermans-Kranenburg and van Ljzendoorn, 2008). Two neurophysin-I (OXT) polymorphisms, rs2740210 and rs4813627, were correlated with baby-talk

vocalizations during mother-infant play (Mileva-Seitz et al., 2013) and polymorphism by early caregiving consequences arose for maternal instrumental care. An investigation of 323 parents, and nonparents showed that vulnerability alleles of the *OXTR* (rs2254298, rs1042778) and *CD38* (rs3796863) loci were associated with decreased parental touch and the interaction of increased plasma OXT and low-vulnerability *CD38* SNPS were associated with longer times of parent-baby gaze synchrony. Parents who described higher quality caregiving in childhood had higher plasma OXT, low-risk *CD38* alleles, and were characterized by more touch toward their own infants (Feldman et al., 2012). In a longitudinal study of parents and their firstborn infants across the first three years of life, parents' behavioral synchrony at 1 and 6 months and mothers' *CD38* SNP were associated with children's social reciprocity during playings with their dearest friend at 3 years, indicating that the transfer from parent-infant attachment to attachment with close friends is supported by OXT- pathway loci enabled by parenting behavior (Uzefovsky et al., 2012). Persistence in attachment security from one year to 26 years was moderated by *OXTR* rs53576; solely among GG homozygous individuals was infant attachment security related to attachment to the agent's romantic partner in adulthood (Lee Raby et al., 2013).

OXTR has also been investigated in connection with parents' brain patterns. Two *OXTR* SNPs (rs1042778, rs53576) were associated with brain responses to child stimuli in the orbitofrontal cortex, anterior cingulate cortex, and hippocampus; the rs53576A allele correlated with positive parenting and with activations in these areas (Michalska et al., 2014). Similarly, only *OXTR* rs53576GG homozygotes preferred infant faces after OXT administration (Marsh et al., 2012) and displayed greater reactivity to cry sounds,

except among those reporting high depressive symptoms (Riem et al., 2011). Finally, assessing mothers' and nonmothers' event-related potential response to infant and adult faces of strong and mild intensity, mothers with *OXTR* rs53576GG genotype showed early-latency differential frontal response to intense facial expression, particularly infants' faces, suggesting that differential brain responses to infants' and adults' emotional cues are mediated by OXTR (Peltola et al., 2014). In a family-based study, *OXTR* rs53576AA homozygous mothers were less warm toward their children (Klahr et al., 2015). African- American adults with the *OXTR* rs53576G genotype coupled with more constructive childhood memories reported greater positive affect and resilient coping (Bradley et al., 2013). The *OXTR* rs2254298 A allele was associated with infant attachment security but only in non-Caucasian infants (Chen et al., 2011). Maltreated *OXTR* rs53576GG homozygous adolescents reported more internalizing symptoms, with no allelic effect on nonmaltreated children, suggesting that *OXTR* rs53576GG homozygotes may be more attuned to negative rearing experiences. These findings indicate that OXTR effects are partly mediated by early environment and the more efficient genotype may open children to greater susceptibility to contextual influences

5.5. ADP ribosyl-cyclases (CD38/CD157), social skills and friendship

The reason that some people look for social contacts while others avoid such contact has important implications for wellness. Some investigations indicate that oxytocin (OXT), the most prominent of human social hormones, and CD38 that enables OXT release, add to individual variation in social skills from high levels of social involvement to virtually total avoidance that distinguish autism spectrum disorder. To characterize

the neurochemical mechanisms of sociality, CD38 expression of blood leukocytes (PBL) was examined by us in Han Chinese university students (Chong et al., 2017). First, CD38 mRNA levels were shown to be associated with lower Autism Quotient (AQ) scores, showing greater social skills. AQ measures autistic traits including the inclination and deftness required for successful social interactions with others. Second, three *CD157* eQTL SNPs in the CD38/CD157 gene were correlated with CD38 transcription. CD157 is a paralogue of CD38 and is next to it on chromosome 4p15. Third, correlation was also seen between the three CD157 eQTL SNPs adjusting CD38 expression and AQ. Fourth, combining plasma OXT and *CD157* eQTLs further demonstrated the association. In the entire model, CD38 expression, *CD157* eQTL SNPs and circulating OXT totally explain a notable 14% of the variance in sociality. Fifth, the ecological validity of this study was shown by the finding that people with greater PBL CD38 expression have more friends, in particular for men. Additionally, *CD157* sequence differences are correlated with scores on the Friendship questionnaire. Altogether, this investigation by singularly leveraging a number of measures uncovers important elements in the oxytocinergic pathway supporting non kin sociality, friendship and uncovers a likely pathway explaining the transition from non-clinical behavior to psychopathology.

Our study (Chong et al., 2017) indicates that lymphocyte CD38 transcription is correlated with AQ scores in 214 normal Singaporean Han Chinese university students, significantly advancing our previous observation in transformed B cells cells lines taken from Israeli ASD subjects (Lerer et al., 2010; Riebold et al., 2011). In the present investigation, CD38 expression enabled to recognized eQTLs across the entire the

CD38/CD157 loci and especially *CD157* eQTL SNPs independently correlation with AQ scores in a group of 1327 university students. Additional proof of the functionality of *CD157* polymorphic SNPs, and its function in the oxytocinergic gene pathway, is demonstrated ~~n~~ by a significant eQTL SNP correlation with plasma oxytocin measurements in 1065 university students. CD38 expression, CD157 eQTL SNPs and plasma, OXT measurements that account for a vigorous 14% of the variance in social skills overall in the group we studied. Notably, our all-encompassing model (expression, eQTL DNA variation and circulating hormone measures) is a significant improvement over present behavioral genetic gene correlation studies where recognized polymorphisms make up for only ~1% of the variation, and generally, of the variance. It is important that ecological validity for these observations is shown by the significant correlation seen between self-reported number of friends, the expected outcome of honed social skills, and the main independent variables in our regression model. Notably, PBL CD38 expression is correlated with the subject's self-reported number of friends. Men with elevated CD38 expression have significantly greater number of friends. This sex effect reflects experiments in vole and mice models of sociality (Lukas and de Jong, 2015). Also, *CD157* sequence variance is correlated with embarks on the Friendship Questionnaire. Overall, from myriad points of view, viz. DNA eQTL SNP sequence variation, gene expression, psychological pencil and paper tests, biomarkers (SNPs and peripheral OXT) and real-life social relationships the current investigation endorses the ever growing standing of oxytocinergic pathways in molding social and communication skills in non-clinical behavior as well as mental illness.

Our study (Chong et al., 2017) uses a blood genomics approach to complement genetic association studies adds to a growing series of investigations that leverage gene expression in lymphocytes to probe the functional genome and reap information beyond simple sequence variations, see (Kurian et al., 2011; Niculescu et al., 2015) among many. There appear to be several views of how best to interpret and use findings related to differences in gene expression in peripheral blood that are correlated with behavioral phenotypes. One view is that lymphocyte gene expression to some extent reflects parallel expression in brain and hence blood expression in part indexes brain expression (Sullivan et al., 2006). An alternative and complementary view suggests that immune involvement contributes to risk for psychopathology and gene expression in lymphocytes is hence not a mere biomarker indexing brain expression, but contributory to etiology. Finally, our study (Chong et al., 2017) shows that ADP ribosyl-cyclases (CD38/CD157), which are obligatory mediators of brain oxytocin release, are at the hub of a complex molecular pathway, which likely includes purinergic and immune signaling pathways that altogether partially determine the skills required to make and preserve friendships. Future studies focused on immune markers such as CD38/CD157 that have been co-opted to serve functions in the brain would appear to be a fruitful path forward towards a more comprehensive understanding of the full range of human sociality.

5.6. **Love and Marriage (Pair Bonding)**(Norman et al., 2010; Young and Wang, 2004)

The most head-line catching characteristic of the oxytocin nonapeptide is its association with ‘love’, pair-bonding and affiliative behaviors (Bachner-Melman and Ebstein, 2014).

Feldman and her associates showed the importance of OXT during the initial stages of romantic attachment (Schneiderman et al., 2012). examined plasma OXT in 163 young adults: 120 new lovers (60 couples) three months after the initiation of their romantic relationship and 43 non-attached singles. Twenty-five

of the 36 couples who stayed together were seen again six months later. Couples were observed in dyadic interactions and were each interviewed regarding relationship-related thoughts and behaviors. OXT plasma levels were significantly higher in new lovers compared to singles. These high levels of OXT among new lovers did not decrease six months later and showed high individual stability. OXT correlated with the couples' interactive reciprocity, including social focus, positive affect, affectionate touch, and synchronized dyadic states, and with anxieties and worries regarding the partner and the relationship, findings which parallel those described for parent—infant bonding. OXT levels at the first assessment differentiated couples who stayed together six months later from those who separated during this period. Regression analysis showed that OXT was correlated with interactive reciprocity independent of sex, relationship duration, and the partner's OXT. Findings suggest that OXT may play an important role at the first stages of romantic attachment and lend support to evolutionary models suggesting that parental and romantic attachment share underlying bio-behavioral mechanisms.

In 2013, a study published by Steele and colleagues reported the results of a discovery and a replication study, each involving a double-blind, placebo-controlled, within-subject, pharmaco-functional Magnetic Resonance Imaging (MRI) experiment with 20 heterosexual pair-bonded male volunteers (Scheele et al., 2013). In both experiments,

intranasal OXT treatment (24 IU) made subjects perceive their female partner's face as more attractive compared with unfamiliar women but had no effect on the attractiveness of other familiar women. This enhanced positive partner bias was paralleled by an increased response to partner stimuli compared with unfamiliar women in brain reward regions including the ventral tegmental area and the nucleus accumbens (NAcc). In the left NAcc, OXT even augmented the neural response to the partner compared with a familiar woman, indicating that this finding is partner-bond specific rather than due to familiarity. Taken together, these results suggest that OXT could contribute to romantic bonds by enhancing their partner's attractiveness and reward value compared with other women.

In 2014, researchers published findings in the journal *Emotion* (Cardoso et al., 2014) suggesting accurate identification of emotion in faces, based on agreement with a normative sample, was impaired in the intranasal OXT group relative to placebo. No such effect was observed for tests using nonsocial stimuli. In line with the social salience hypothesis concerning the effect of intranasal oxytocin on social cognition (Averbeck, 2010; Bartz et al., 2011; Shamay-Tsoory and Abu-Akel, 2016) the authors predicted that intranasal oxytocin would enhance the perception of emotion in faces, but not the perception of emotion in nonsocial stimuli. Consistent with their prediction, intranasal oxytocin increased ratings of intensity of all emotions perceived in faces. Consequently, this effect decreased the accurate identification of emotions in faces on the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), where the identification accuracy of an emotion is based on agreement with a normative sample.

As expected, no effect of intranasal oxytocin on ratings of emotion in nonsocial stimuli (designs and natural scenes) or on a task of abstract verbal reasoning about emotion.
In an interesting study (Bartels and Zeki, 2004) the authors employed functional imaging (fMRI) to examine brain activity in mothers viewing pictures of their own and of acquainted children, and of their best friend and of acquainted adults as additional controls. The activity specific to maternal attachment was compared to that associated to romantic love described in an earlier study of these authors and to the distribution of attachment-mediating neurohormones established by other studies. Both maternal and romantic 'love' or attachment activated regions specific to each, as well as overlapping regions in the brain's reward system that coincide with areas rich in oxytocin and vasopressin receptors. Both deactivated a common set of regions associated with negative emotions, social judgment and 'mentalizing', that is, the assessment of other people's intentions and emotions. The authors interpreted these findings to mean that human love and attachment implements a push–pull mechanism that minimizes social distance by minimizing networks used for critical social assessment and negative emotions, while individuals form attachments mediated by the reward circuitry, offering insights into the power of love to motivate and exhilarate.
The reader is referred to an excellent review by (de Boer et al., 2012) that thoroughly covers the biological perspective on human romantic love.

6. Oxytocin and Gut Microbiota

In rodents, OXT mediates antidepressant-like effects and low OXT levels positively correlate with depressive and stress-like phenotype and changes in the gut bacterial

(Matsunaga et al., 2009; Norman et al., 2010). Interestingly, there is a strong interaction between stress and the gut microbiota composition. Reversible effects were observed by feeding mice with *L.reuteri* which were dependent on vagal signaling that blunted *Lactobacillus* plasma and hypothalamic OXT(Buffington et al., 2016). A recent review by Lach and colleagues covered the main reported studies on the association of anxiety, depression and the microbiome (Lach et al., 2018). In humans, people with autism reported digestive problems and this might be related to OXT (Tomova et al., 2015). Mounting evidence indicates that genetic and epigenetic variations in the OXTR gene are related to autism spectrum disorders (Jacob et al., 2007). Future research in this field might provide novel understanding at both mechanistic and therapeutic level that might aid in the treatment of mood disorder and autism as well as *further genetic research is needed to evaluate the relationship between OXT and CD38 and autism spectrum disorders*.

7. Oxytocin in the context of independent and interdependent cultures

Transcultural and imaging genomic studies provide a great deal of evidence that neural correlates of multiple cognitive and affective processes are shaped by both cultural milieu and genetic background (Han and Ma, 2015; Kitayama et al., 2016, 2014; Kitayama and Uskul, 2011; Luo et al., 2015; Sasaki, 2013).

Luo and his colleagues (Luo et al., 2015) investigated whether and how *OXTR* rs53576 interacts with interdependence - a key dimension of cultural orientations that distinguish between East Asian and Western cultures - to affect human empathy that underlies altruistic motivation and prosocial behavior. Experiment 1 measured interdependence,

empathy trait and *OXTR* rs53576 genotypes of 1536 Chinese participants. Hierarchical regression analyses revealed a stronger association between interdependence and empathy trait in G allele carriers compared with A/A homozygotes of *OXTR* rs53576. Experiment 2 measured neural responses to others suffering by scanning A/A and G/G homozygous of OXTR rs53576 using functional magnetic resonance imaging. Hierarchical regression analyses revealed stronger associations between interdependence and empathic neural responses in the insula, amygdala and superior temporal gyrus in G/G compared with A/A carriers. Their results provided the first evidence for gene x culture interactions on empathy at both behavioral tendency and underlying brain activity.

8. Conclusions

OXT and CD38 are emerging as paramount human social hormones contributing significantly to human affiliative behaviors, including social skills, human pair bonding, and friendship. Evidence from many sources, including imaging studies, electrophysiology, genetics, pharmacogenetics and plasma measures of OXT, all support the importance of these two molecules in a wide range of human social behaviors. Our review discusses the novel social salience hypothesis of oxytocin action, which is an interesting view of how this molecule influences human social behavior. In addition, this review covers the important role of oxytocin in trust related behavior, parenting and parental attachment. Affiliative behaviors leading to love are complicated and well-illustrated by the song “Love and Hate” by Michael Kiwanuka found on YouTube https://www.youtube.com/watch?v=aMZ4QL0orw0.

Three interesting publications have recently provided novel potential avenues for future research on CD38 and oxytocin. Yamamoto and Higashida demonstrated in a recent Communications Biology article that the receptor for advanced glycation end-products (RAGE) is oxytocin's binding protein and enables its transport to the brain (Yamamoto et al., 2019). In addition, Zhao and colleagues demonstrated that SARM1 catalysis was similar to CD38, despite having no sequence similarity. Both catalyzed similar set of reactions, but SARM1 had much higher NAD-cyclizing activity, making it more efficient in elevating cADPR. (Zhao et al., 2019). Lastly, as highlighted by Liu and colleagues, SARM1 causes cortical and axonal neurodegeneration, however, whether NAD+ loss and the associated defects in energy metabolism are the primary effectors of axonal degeneration is controversial. In addition, how nicotinamide mononucleotide (NMN) relates mechanistically to axon degeneration, and presumably SARM1 activation, remains unresolved (Liu et al., 2018). In conclusion, investigations of OXT and CD38 are constrained by the complexity of the affiliative behavioral phenotype and the many confounds that contribute to interpreting experiments that are context dependent. The current review presents what we expect is a balanced view of the state of knowledge of OXT on human sociality.

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Figures legends

Figure 1. Oxytocin induced oxytocin release
Oxytocin (OXT; *yellow circles*) stimulates oxytocin receptors (OTR). Subsequently, the $G_{q/11}$ type G protein and phospholipase C (PLC) are activated, resulting in formation of inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). Stimulated protein kinase C (PKC) activates CD38 and increases formation of cADPR from β-NAD^+ inside or outside cells. cADPR activates Ca^{2+} influx TRPM2 cation channels. 2-Aminoethoxydiphenyl borate (2-APB) inhibits TRPM2 channels. IP3 induces mobilization of Ca^{2+}. TRPM2 (Transient Receptor Potential Cation Channel Subfamily M Member 2) mediates Ca^{2+} influx, which also stimulates Ca^{2+} mobilization through ryanodine receptor Ca^{2+} release channels as a cofactor together with cADPR. These Ca^{2+} ions (*filled circles*) increased by Ca^{2+} amplification mechanisms stimulate OXT (*yellow*) release into the brain, which is an essential step for social memory and social behavior.

Figure 2. Structure of OXT and AVP nonapeptides

Fig. 3. Schematic model of the structure of the OXTR and its interaction with the ligand
The endogenous ligand, the nonapeptide OXT, is shown at the top left with residues numbered 1–9. The OXT receptor (shown in blue) is depicted in its proposed interaction with the ligand (shown in red). The seven putative trans- membrane domains are indicated by Roman numerals. Residues referred to in the text are indicated by numbers referring to the amino acid sequence of the human OXT receptor. The filled yellow circle on transmembrane domain III denotes residues L114, V115 and K116; reproduced by Zingg HH, Laporte SA (2003) The oxytocin receptor. *Trends Endocrinol Metab* 14(5):222–227.

Figure 4. In the Trust Game the 1st Player sends amount Y to Experimenter who in turn sends triple the amount to Player 2. At this point, Player has the option to send any fraction of amount received back to Player 1. Berg, Joyce, Dickhaut, John, & McCabe, Kevin (1995), Games and Economic Behavior 10: 122-142

Figure 1

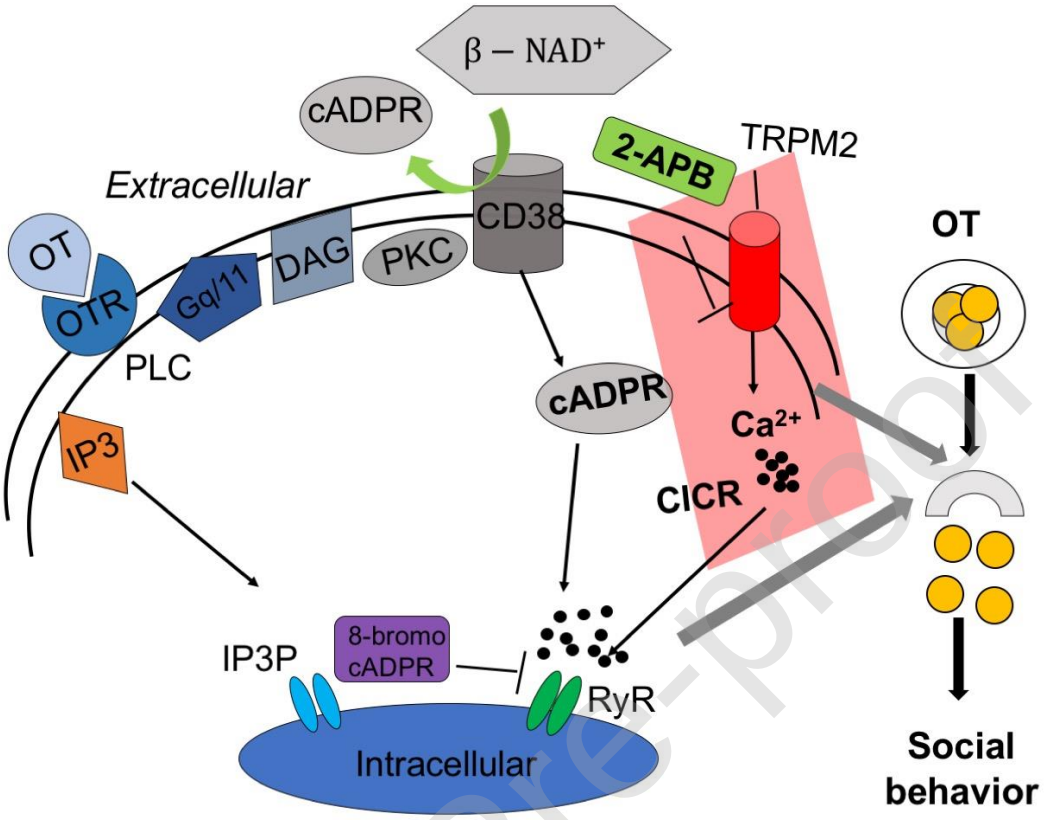

Figure 2

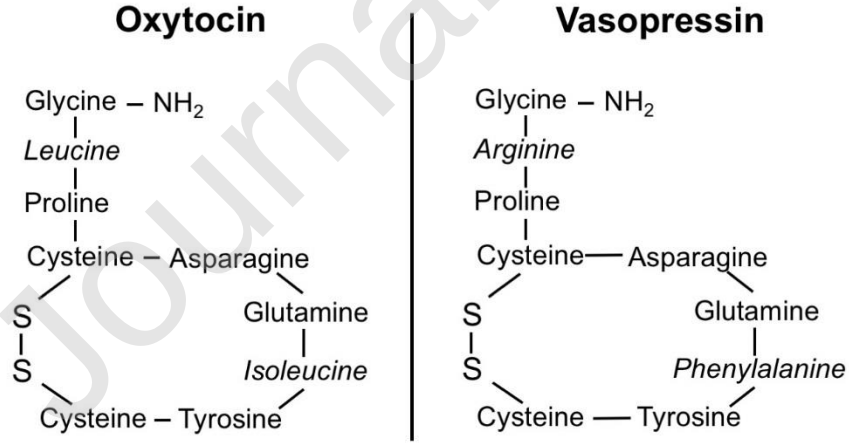

Figure 3

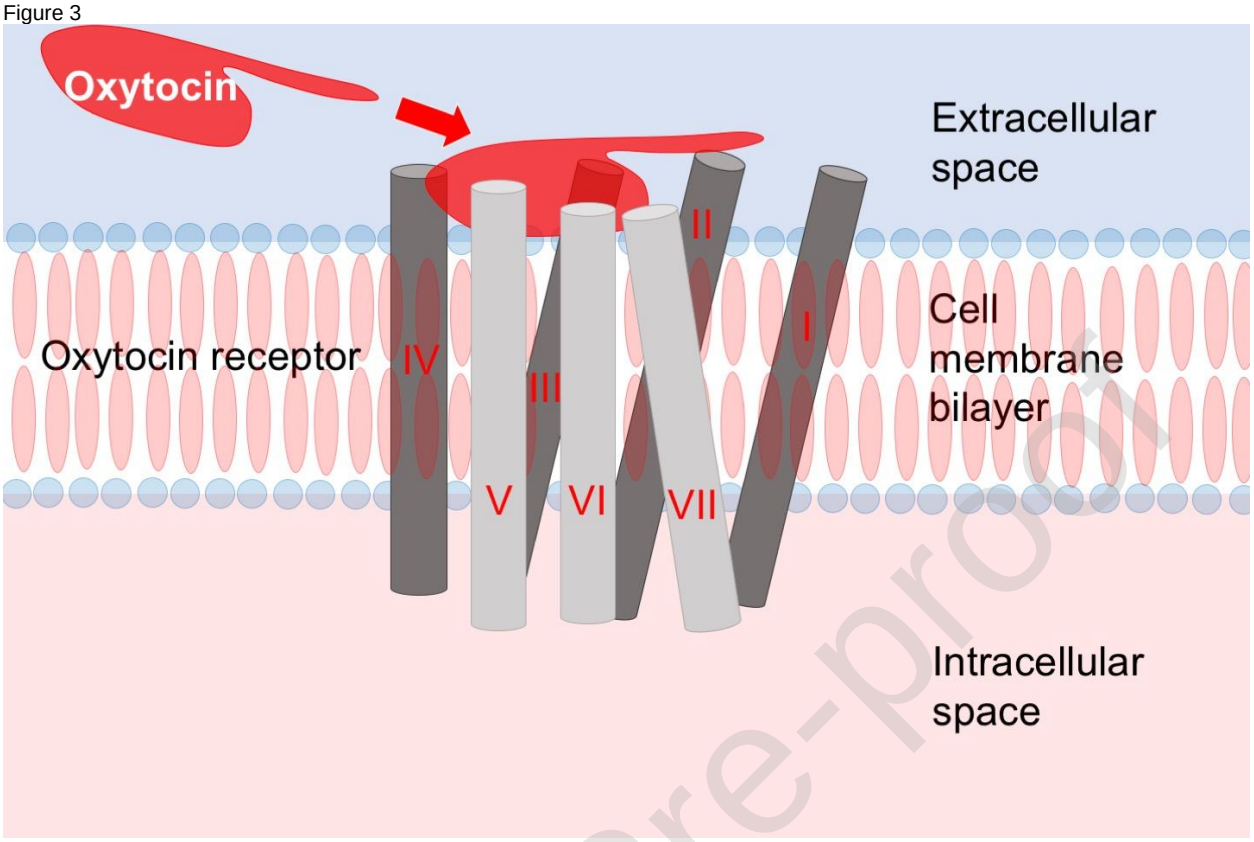

Figure 4

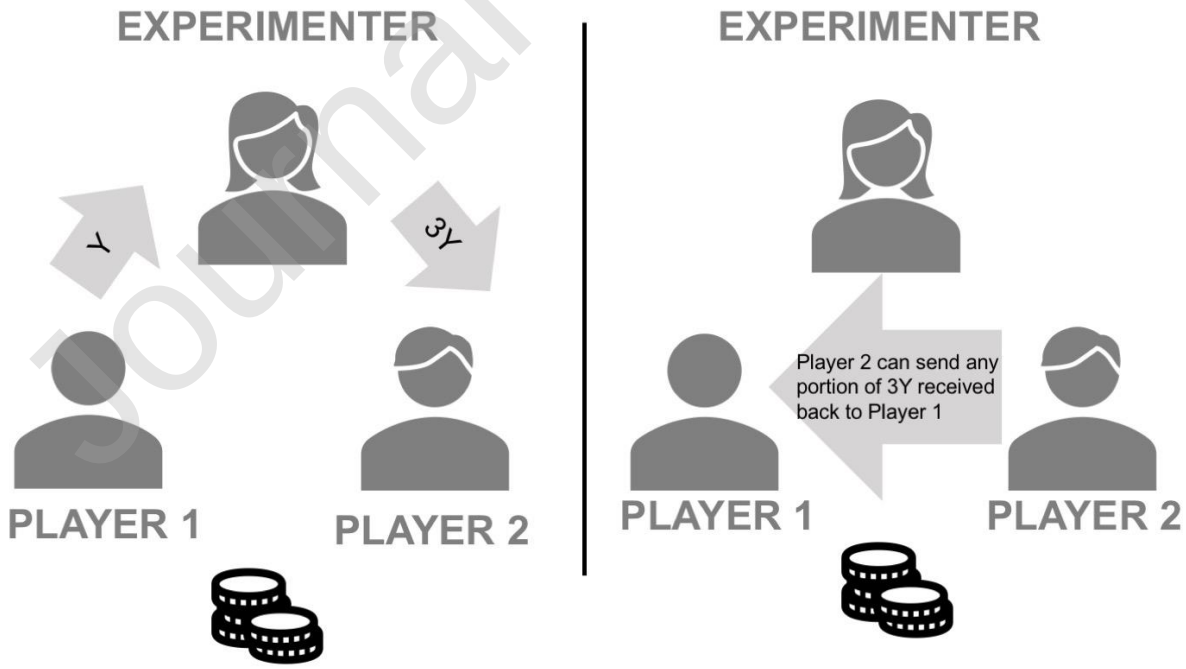

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Table 1
Title: Recent studies of the mechanism of action of oxytocin and CD38 on affiliative behaviors

ASSESSMENT	KEY WORDS	SNP	LOCATION	ACTION	PHENOTYPE	SAMPLE SIZE	REFERENCE
Cytokine levels	Wound healing; Oxytocin; Cytokines; Couple behavior; TNF-alpha.			OXT reduced TNF- levels 24 h post wounding); Friendly behavior during couple interaction predicted lower TNF-alpha levels at 24 h post wounding; OXT and friendly behavior interacted to further reduce TNF-alpha.	**Wound healing**	80 couples 160 individuals	(Aguilar-Raab et al., 2019)
fMRI; Endogenous Salivary OXT; INA OXT	Amygdala; Attachment; Autism spectrum disorders; Hippocampus; Oxytocin; Resting-state fMRI.			Peripheral OXT corr. with secure attachment; no corr. with ASD symptoms; neural level, >>endogenous OXT with << interregional functional coupling between amygdala and hippocampus; INA OXT - further reduction in amygdala–hippocampal connectivity.	**Autism Attachment**	40 patients OXT group, n = 22; placebo group, n = 18); 24 IU OXT INA	(Alaerts et al., 2019)
Conduct Problems OXTR genotype	oxytocin receptor; gene, rs53576; maltreatment; conduct problems; gene–environment; interaction.	OXTR rs53576	intronic	Association between maltreatment and conduct problems independent of the genotype; **F** G allele carriers >> conduct problems & >>	**Maltreatment**	691 boys and 900 girls	(Andreou et al., 2018)

				among maltreated group			
Mother-child interactions; Toddler self-regulation (assessed through compliance and vagal withdrawal during a toy clean-up task @ 2 years of age. Toddlers' electro-cardiogram – vagal tone	GxE; infancy; maternal sensitivity; RSA; self-regulation.	OXTR rs53576, D2 dopamine receptor gene DRD2 TaqIA, rs1822497		diathesis-stress patterns, predicting compliance for the GG genotype group, and predicting physiological regulation (vagal withdrawal) for the AA/AG genotype group	**Early maternal sensitivity; Toddler self-regulation**	6 months and 1&2 year of age (N = 186)	(Augustine et al., 2018)
SMART PHONES	Personality; neuroscience.	rs2268498 ***OXTR***	Adjacent to. promoter	Active contact; incoming calls	**Social network size**	N=117 (77 F)	(Sariyska et al., 2018)
ECOLOGICAL MOMENTARY ASSESSMENT (EMA)	social buffering; stress; oxytocin; ecological momentary assessment (EMA).	rs2268498 rs53576 ***OXTR***	~ promoter intronic	CG hap = **NO** social buffering; TG & CA significant social buffering	**Social stress**	N=317 (77% F)	(Sicorello et al., 2019)
QUESTIONNAIRES	GxE; Social anxiety; Parenting; Diathesis-stress; Plasticity genes.	rs4813625 rs2770378 ***OXT*** Neurophysin 1 prepro-peptide	Intron, n.c. downstream	Parenting style x OXTR X Differential *susceptibility* framework for rs4813625; rs2770378 the results indicated a *diathesis–stress* type of interaction	**Social anxiety adolescents**	N=1,359 (59.4% F)	(Olofsdotter et al., 2018)
QUESTIONNAIRES Relationship Assessment Scale (RAS)] & sexual attitudes and behaviors [Sociosexual Orientation	romantic relationship; social networks; social neuro-peptides.	***OXTR*** rs2228485 **RMET** non-linear (domdev P = 0.049) **SOI-R SCORES**	rs2228485 Synony-mous coding variant AAC leucine G>A; rs237887	1.Non-linear relationship with SOI-R scores 2.dyadic relationship 3. Wider network	**Sexual relationships**	757 white British (423F)	(Pearce et al., 2017)

Inventory Revised & (SOI-R)] more generally		rs237887 rs2268490 rs2254298 rs13316193 rs53576 rs237897 rs4686302 **WIDER NETWORK** personal network size, OXTR rs237887	intron variant				
REPLICATION STUDY: PEARCE ('17) QUESTIONNAIRES RMET; EQ; ECR experience close relationships; SOI-R dyadic relationships; social network size; Relationship Assessment Scale (RAS); Other in Self (IOS) scale		***OXTR*** 10 SNPs Additivity; heterozygote advantage; dominance. SNP level analysis no correction multiple testing		rs237887 related to SOI-R anxious attachment; rs53576, rs237887 in suclinical sample & RMET & IOS	**Social Disposition, Romantic Relationships & Social Networks**	first sample had mental illness (N = 140, 95 female), Non-white (N = 66, 33 F) no mental illness	(Pearce et al., 2018)
Cyberball game Emotional responses (7 self-report Questionnaires; EEG	Social salience; hypothesis SSH; Late positive potential; intranasal OXT.			Syntocinon® Novartis 40 IU in 1 ml; No main effects of oxytocin on the self-reports of rejection or the LPP in exclusion trials were found; correlation	**Social exclusion**	90 F	(Petereit et al., 2019)

				LPP amplitude & self-reports of rejection is observed in the placebo condition, but is << in OXT; results show that the link between neural and affective reactions to social exclusion is eliminated by oxytocin??			
Hot sauce White noise Trait anxiety questionnaire	Oxytocin; Aggression; Provocation; Anxiety.			24 IU 3 puffs Syntocinon® Novartis OXT >>aggression in response to provocation in low anxiety people; no difference in group and out group	**Aggression**	56 M Germans	(Pfundmair et al., 2018)
Cutaneous wound healing; Skin biopsy assay; OXT knock out; Vagotomies	Wound healing; Probiotics; Mice; oxytocin.	plasma oxytocin levels in our female C57BL/6 wt mice & significant systemic elevation of OXT in animals drinking L. reuteri (from human milk) daily		Probiotics L. *reuteri*; ingestion in water-drinking- of a lactic acid bacterium presumably upregulates OXT in hypothalamus via vagus nerve	**Wound healing Activate host CD4+Foxp3+CD25+ immune T regulatory cells**	12 animals in each group	(Poutahidis et al., 2013)
Urinary OXT levels Chimpanzee wild Only males	Oxytocin; Reconciliation; Bystander affiliation; Relationship repair.	URINE		Oxytocin system is activated in reconciliation with or without bystander post-conflict	**REPAIRING RELATIONSHIPS POST-CONFLICT RESOLUTION**	10 males ~2600 observatons	(Preis et al., 2018)

				affiliation or affiliation alone; **Supports 'valuable relationship hyp'**			
voxel x voxel volumetric gene expression maps; 3 genes: OXTR, CD38 and OXT; Each brain was sampled in 363–946 distinct locations; Agilent 8 × 60 K cDNA array chip.				Expression of the three selected oxytocin pathway genes was enriched in subcortical and olfactory regions and there was high co-expression with several dopaminergic and muscarinic acetyl- choline genes	**distribution of OXT, OXTR, and CD38 mRNA across the human brain**	6 donor brain; custom	(Quintana et al., 2019a)
Exploration time (anxiety)- dark light preference; F exposed to coercive M vs F exposed to F-- decreased social preference for coercive males and increased social preference for conspecific female Results support social salience hypothesis	Oxytocin Isotocin; Social salience; Poeciliid; Social cognition; Social; discrimination; Sexual conflict; Social decision-making; Anxiety; Exploration.			Injected IT in F Forced mating system where M coerce F to mate Isotocin (IT) > anxiety F <time with males <<Social behavior towards M	**Female decision making & anxiety behavior**		(Ramsey et al., 2019)
Trier Social Stress Test	Cannabis Oxytocin; Self-administration; Sex			40 IU INA OXT-TSST condition, positive subjective effects were	**Stress reactivity**	31M 32F CANNABIS USERS	(Reed et al., 2019)

	differences; Stress.			lower and negative subjective effects were higher in women compared to PBO administration and compared to men			
activation of PVH-OT neurons recording of OT neurons in awake mice using two-photon calcium imaging.	Social behavior; Male mice; PVN hypothalamus.			chemogenetic activation of OT neurons within the paraventricular nucleus of the hypothalamus (PVH) of male mice (OT-Ires-Cre**) enhanced social investigation during a social choice test** *Shank3b* knock-out (KO) mice (ASD). Male *Shank3b* KO mice showed a marked reduction in PVH-OT neuron number and administration of an OT receptor agonist improved social deficits.	**Social behavior Social salience** PVH-OXT neurons encode social and non-social stimuli, suggesting that PVH-OT neurons may act to convey social salience of environmental stimuli.		(Resendez et al., 2020)
(Re-analyzed data from previous study} fMRI & INA OXT iterated Prisoner's Dilemma - same sex partner; Focus on *social behavioral*	Nucleus basalis of Meynert; nucleus accumbens; lateral septum; Human Social Behavioral Neural Network (SBNN).			OT induced widespread increases in functional connectivity in response to positive social interactions **among men** and widespread decreases in functional connectivity in response to	Dyadic social interaction **Reciprocal altruism**	intranasal OT (n = 100), 20 IU intranasal AVP (n = 100), or placebo (PL, n = 104) 50% F Emory students	(Rilling et al., 2018)

neural network (SBNN)				negative social interactions **among women**			
Immunohisto-chemistry	Axons; cingulate; insula; neuropeptides; primates.			OT- and AVP-containing fibers in cortical regions relevant to social cognition **in humans, chimpanzees, and rhesus macaques**	**Social cognition**	3 M human brains PM Chimpanzee 1M 2F Rhesus 3M 2F	(Rogers et al., 2018)
Food reward Pairing two individuals from the same social group and alternately ask them to complete a task in order to obtain a food reward Vary quality, effort reward =Paradigm	Domestic dogs; Inequity aversion; Oxytocin; Decision latency; Affiliation.			40 IU <sensitive to inequity following OXT >attention to partner <decision time	**Inequity aversion**	8F 6M	(Romero et al., 2019)
Novel arena with 2 unfamiliar trainers	Exploration; play; oxytocin; cortisol; domestic dog.				Exploration Play behavior		(Rossi et al., 2018)
fMRI by measuring the amplitude of low-frequency fluctuations (ALFF)= intrinsic spontaneous neuronal activity.	Sex differences; Resting state; Schizophrenia; Oxytocin; Vasopressin ; fMRI.			Measured [AVP] and [OXT] F SCZ lower [OXT] were associated with lower ALFF in frontal and cerebellar cortices; female C [AVP] levels were inversely associated with ALFF in the frontal cortex; male SCZ < [OXT] associated with < ALFF in the posterior cingulate; < [AVP] associated with	Schizophrenia (SCZ)	35 patients (23 M) & 60 controls “C” (24M)	(Rubin et al., 2018)

				<ALFF frontal cortex ETC			
EEG INA OXT on neural oscillations (delta, theta, alpha, beta) and their coupling during	INA OXT; Neural oscillations; Cross-frequency; coupling.			24 IU OXT INA OXT << cross-frequency **coupling** across the slow and fast waves assessed; OXT << delta-beta, delta-alpha, theta-alpha, and theta-beta coupling.	Previous studies: Oscillations linked to specific emotional and cognitive states	Healthy nulliparous women (N=23) Mixed ethnicity	(Rutherford et al., 2018)
Depression, anxiety, and eating disorder symptoms QIDS-CR quick inventory (SIGH-A (Hamilton structured interview); (SCID-RV DSMIV (YBC-EDS) eating disorder survey: self report; fMRI	social cognition; fMRI; eating disorders; neuroimaging; self-perception; depression; anxiety; endo-phenotypes.	**rs2254298 rs53576**	Intron variants	**rs2254298** "A" rs2254298 (2 AA and 10 AG) <<activation posterior cingulate cortex and medial prefrontal cortex for social stimuli; >> negative connectivity between the posterior cingulate and the occipital lobe relative to the GG; **rs53576** no effect	Social stimuli: visuospatial l condition, the cue was "Bumper cars: Same weight?" and in the social attribution condition, the cue was "People: All friends?"	Women Anorexics N=49 With or recovered	(Sala et al., 2018)
3rd party decision making paradigm: participants could sacrifice their own resources to modulate the monetary gains and losses **of in- and out-group members**. interactions in naturalistic inter-group conflict;	Decision-making; Empathy; Inter-group conflict; Oxytocin; Social groups; Spatio-temporal brain dynamics.			24 IU OXT (OXT condition: N = 43; placebo condition: N = 43) **Behavior**: OXT eliminated the reduction in out-group gains –particularly in individuals with low emotional empathy; **ERP:** oxytocin replaced a neuro-physiological process associated with the negative valuation of out-group gains via a process	Inter-group conflict	N=86 M Ss: rival soccer clubs or supporters of opposing political parties.	(Schiller et al., 2020)

ERP event related potential				associated with (+) valuation			
Total sleep deprivation (1 night) QST battery Quantitative sensory testing – thermal pain, pin prick devices; Cold pressor test	Sleep deprivation (SD); Pain sensitivity; Oxytocin; Plasma			Extracted plasma; Saliva cortisol plasma [OXT] >> sleep deprived F, not M; << heat pain thresholds corr.>> plasma [OXT], no effect cold/mechanical pain; SD F >plasma [OXT] lower pain inhibition p<0.1); (+) corr. between anxiety-scores and plasma [OXT]-sex dependent; No change in cortisol due to SD		20 students 10M All F on contraceptives	(Schuh-Hofer et al., 2018)
Voles housed in divided cages with possibility of food sharing (FS) High-fat diet (HFD) and low-fat diet (LFD) Serum hormones, blood glucose, lipids	INA OXT; High and low- fat diet; Food sharing; Voles; Obesity.			8 IU per kg HFD > weight gain HFD + housing with LFD fed animals = inter-mediate weight gain & FS **Chronic OXT INA elicits weight loss in part by food sharing for the LFD partner**	Energy intake Effect of social context Predisposition to diet induced obesity (DIO)	Prairie voles	(Seelke et al., 2018)
12-item short version of Buss and Perry Aggression Questionnaire; Adolescent Self-Rating Life Events Checklist	Aggression; OXTR; rs53576; Han Adolescents; Stress.	rs53576	intronic	AA OXTR rs53576 homozygosity corr. with > aggression under high life stress conditions		197 Han adolescents 143 Saliva DNA	(Shao et al., 2018)

Immunochemistry and single cell PCR	OXTR neurons; Mouse; Preoptic area; anteroventral periventricular nucleus (AVPV); Estrogen; Sexual dimorphism.			in M no OXTR-Venus cells in anteroventral periventricular nucleus (AVPV) within the MPOA **but present in F**; expression of OXTR in AVPV is F specific-**estrogen dependent**	OXTR expressing neurons in mouse preoptic (POA)		(Sharma et al., 2019)
Glucocorticoid levels, oxidative damage, telomere length, and anhedonia	Oxytocin; Telomeres ;Oxidative stress; Stress; Social support; Aging.			six weeks of chronic isolation > glucocorticoid levels, oxidative damage, telomere degradation and anhedonia; Daily OXT injections in isolated voles prevented these negative consequences.	Damaging effects of social isolation in prairie voles	Prairie voles	(Stevenson et al., 2019)
Group 1 placebo Group 2 Liraglutide Group 3 160 µg/kg/day oxytocin i.p. Group 4 filgrastim i.p.	Doxorubicin; Cardiotoxicity; Liraglutide; Oxytocin; G-CSF Inflammation.			DXR + OXT group had the most preserved tissue integrity; least immune expression level of CASPASE-3; highest ECG QRS wave voltage amplitude; ETC.	Doxorubicin-induced (DXR) cardiomyopathy	40 male Sprague–Dawley rats	(Taşkıran et al., 2019)
label OXTR-bearing cells; Fluorescence images of cortical sections showed striking labeling of CA2 pyramidal cells indicating OXTR present	Hippocampus; Area CA2; OXTR receptor;			experiments revealed a robust modulation of excitatory pyramidal cells in CA2; oxytocin modulation of multiple signaling pathways and diverse cell types operates in coordination to tune the effect of CA2	hippocampal area CA2 neurons intrinsic properties Powerful effect of OXTRs on repetitive firing in CA2 and showed how the bursts arose from	Mice	(Tirko et al., 2018)

				on the hippocampal network	diverse signaling events, ionic mechanisms, and circuit actions operating in concert.		
effects of oxytocin (24 I.U. in 6 puffs of Syntocinon-Spray, Novartis) on self-other distinction on two different processing levels (i.e., lower-level imitation-inhibition and higher-level perspective taking)	Oxytocin; Self-other distinction; Perspective-taking; Imitation; Social approach.			Oxytocin improved visual perspective-taking and thus affected self-other distinction on the cognitive level, but had no effects on self-other distinction on the perceptual-motor level nor on a control task measuring attention reorientation	Distinguishing self-from other-related representations	56 M Ss	(Tomova et al., 2019)
Children exposed to continuous wartime trauma maternal and child's **salivary** immunoglobulin A (s-IgA) and oxytocin (OT), mother-child affiliation	Childhood anxiety disorders; early life stress; maternal behavior; oxytocin; salivary IgA; trauma; war exposure.			War-exposed mothers had higher s-IgA, lower OT, more anxiety symptoms, and their parenting was characterized by reduced sensitivity. Exposed children showed higher s-IgA, more anxiety disorders and post-traumatic stress disorder, and more anxiety symptoms. Path	children's stress reactivity anxiety	(N= 177; exposed; N= 101, controls; N= 76	(Ulmer-Yaniv et al., 2018)
Ss play a trust game **with their mother** and a stranger	Oxytocin; Trust game; Intranasal; Psychopathology. Attachment			24 IU oxytocin (Syntocinon-Spray, Novartis)	attachment-related and non-attachment-related trust	122 adolescents 70% F; Mixed ethnicity;	(Venta et al., 2019)

over the Internet. Trust game modified from Kosfeld (2005); Child Attachment Interview				OXT only affected the trust game behavior of adolescents when attachment security was moderate or low. **Paradoxically**, OXT reduced the investments (Trust) of healthy control subjects		Healthy controls and 75 Ss from urban psychiatric unit - severe emotional and behavioral disorders	
Positive and Negative Syndrome-Scale (PANSS); Diagnostic Interview for Genetic Studies (DIGS); DSM IV; Hamilton; WAIS-III		rs143908202 rs150746704 rs115324487 rs80058195 rs150746704 rs115324487 rs61740241	Cases with rare missense coding SNP variations Synony-mous and NS	carriers < severe negative symptoms (deficits in emotional expression & motivation) & < severe general psychopathology scores (depression & anxiety); lower nonverbal (performance) than verbal intelligence due to deficient perceptual organization & slow processing speed. Greater early trauma exposure (physical & sexual abuse & emotional trauma	Schizophrenia	Five of 48 cases showed rare OXTR variants	(Veras et al., 2018)
OXTR and *AVPR1A* gene expression in blood-peripheral blood mono-nuclear cells (PBMC); ABC, VABS, SRS, and CBCL scores	OXTR; AVPR1A; Blood (PBMC) Gene expression; ABC; VABS; SRS; CBCL scores.			OXTR & AVPR1A >> inter-individual variations;> OXTR (most informative) & AVPR1A expression < Aberrant Behavior checklist (ABc) scores; OXTR expression <	Autism (ASD)		(Voinsky et al., 2019)

				severe behavior and higher adaptive behavior on additional standardized measures; combining the sum expression levels OXTR, AVPR1A, and IGF1 >> strongest corr. with ABc scores; **Unlike OXTR SNPs, OXTR mRNA levels seem to be more informative of ASD severity**			
react to different word categories within a list of successively presented words; After a 24-h delay, memory for all words was tested individually in a surprise recognition memory test; social (with partner) & non-social condition (no partner)				OXT positively affected memory for participants who scored low on attachment dependence (who find dependence on others uncomfortable), but negatively affected memory for high scorers (who are comfortable depending on others). Oxytocin effects were not moderated by social vs. non-social context at encoding	Human memory encoding		(Wagner and Echterhoff, 2018)
Mandarin voles levels of paternal behavior as well as oxytocin (OT) and dopamine-2 type (D2) receptors in the nucleus				These data illustrate that fathering experience (new fathers; experienced fathers) could increase the active components of parental care and alter the	Fathering experience		(B. Wang et al., 2018)

accumbens (NaCC) and medial nucleus of the amygdala (MeA); Paternal behavior: Licking, retrievals & huddling				expression levels of OXTR and DRD2 in a region (NAc & MeA) and time-dependent way (days after birth).			
Single prolonged stress (SPS)+Pavlovian fear conditioning –RAT model of PTSD; abnormalities of fear extinction; pro-inflammatory cytokines. mRNA expression of IL-1β, IFN-γ, and TNF-α in the medial prefrontal cortex (mPFC), hippocampus, and amygdala; plasma OXT, corticosterone, IL-1β, IFN-γ, and TNF-α	posttraumatic stress disorder; single prolonged stress; oxytocin; pro-inflammatory cytokines; tumor necrosis factor α; interleukin 1β; interferon γ.			SPS exaggerated inflammation & fear memory extinction ability; Strengthening OXT signaling may reduce the levels proinflammatory markers → Augment the efficacy of extinction training	core psychopathology of **PTSD**, i.e., **trauma-disrupted cue/contextual extinction learning**		(S.-C. Wang et al., 2018)
Behavior: open field test, tail suspension test, marble burying test and three-chamber social interaction test. Oxidative Oxidative stress:	Autism; Oxytocin; Inflammation; Oxidative stress; Microglia.			OXT improved the behavior with < anxiety, depression & repetitive behavior & ameliorated social interaction; elevated oxidative stress & inflammation alleviated after OXT treatment	Autism-VALPORATE mouse model		(Y. Wang et al., 2018)

tumor necrosis factor-α, interleukin-1β and interleukin-6. activated microglia: immune fluorescence							
CBC, Complete Metabolic Panel, & clinical ratings 24 IU OXT INA versus placebo; Preload & subsequent test meal; Self-reported satiety + preload-test meal paradigm; levels insulin, glucose, & leptin, and measures of taste & smell.	schizophrenia; oxytocin; satiety; leptin; olfaction; gustation.			significant treatment difference was solely for leptin-decrease in leptin in the oxytocin group post-administration, but no time effect or treatment by time interaction.	Self-reported satiety	DSM-IV diagnosis of schizophrenia (N=16).	(Warren et al., 2018)
Use a combination of optical, behavioral and genetic approaches in the larval zebrafish				noxious experience cause activation of Transient receptor potential cation channel; (TRPA1) receptor activation drives both OXT neuron firing & defensive swimming, and both the sensory & motor components of this process are encoded in	Processing of noxious stimuli; Defensive responses to noxious stimuli		(Wee et al., 2019)

				OXT population activity			
METH infusion & in vivo microdialysis in the NAc ± OXT ip 30 min prior to METH.	Addiction; Dopamine; Microdialysis; Social support; Oxytocin.			social housing attenuates escalation of METH intake and reinstatement of METH seeking in female rats; **chronic OT treatment also reduces motivation for METH in isolated and socially housed F. Social housing did not enhance the effects of OT to reduce the motivation to self-administer METH.**	Methamphetamine (METH) intake	Female rats 48 rats (24 individually housed and 24 paired)	(Westenbroek et al., 2019)
Interpersonal Reactivity Index (IRI)); MRI scan				24 IU OXT INA; **functional connectivity (FC)** maps in left **temporoparietal junction** (lTPJ) and right TPJ; OXT > connectivity between rTPJ and default attention network (DAN); < FC between lTPJ and medial prefrontal network (MPN); **empathy trait** can modulate the FC	resting-state functional magnetic resonance imaging	59 right-handed male college students Beijing	(Wu et al., 2018)
40 IU; OXT-Spray, Sichuan Meike Pharmaceutical Co. Ltd, China;	oxytocin; sex difference; mate choice; attraction; infidelity.			oxytocin release during courtship may first act to amplify sex-dependent priorities in		160 Ss 80 M	(Xu et al., 2020)

Facial image rating for fidelity				attraction and mate choice before subsequently promoting romantic bonds			
INA OXT 24 IU OXT (Oxytocin-spray Sichuan Meike Pharmaceutical Co); Ss played a modified online ball-tossing game-Cyberball + $$ rewards & potential to display altruistic & self-interest behaviors	altruism; empathy; oxytocin; orbitofrontal cortex; self-interest.			in the context of competing motivations for exhibiting altruistic or self-interest behavior, OXT >> self-interest associated >> activation in frontal reward areas; OXT did not enhance empathy	Altruistic Self-interest behaviors	82 M Chinese University students	(Xu et al., 2019)
OXT ip 1mg/kg open a door to help a cagemate soaked with water; Pair and Solo groups	Oxytocin; Empathy; Prosocial behaviour; Rats.			OXT→ the Solo group showed helping behavior faster than those in the Pair group; oxytocin→helping behavior are dependent on social context	Helping behavior		(Yamagishi et al., 2019)
in vitro BBB model system: brain capillary endothelial cells; Ager−/− male (RAGE KO) mice lacking RAGE; **CSF OXT assayed -** Enzo RIA; **Immunoelectron microscopy** ; **Behavior**: Light-dark transition				behaviours characteristic to abnormalities in OXT signalling are recapitulated in Ager−/− mice: deficits in maternal bonding & hyperactivity; expression of RAGE on capillary endothelial cells of the blood-brain barrier (BBB) is both necessary and sufficient for the transport of	OXT transport into Brain		

test; Open field test.				oxytocin into the brain; [OXT] elevated 3rd ventricle, cisterna, amygdala, PVN of WT but not Ager−/− mice			
pharmaco-fMRI study 40 IU; Oxytocin Spray, Sichuan Meike Pharmacy Co Ss instructed to make approach responses to positive social or non-social stimuli (e.g., happy friends meeting or beautiful landscapes) or avoid responses to negative social and non-social stimuli	Oxytocin; Approach /avoidance; Anterior insula; Positive social stimuli.			OT < activity in the right striatum irrespective of response (approach/avoid-ance) & social context, suggesting an inhibitory effect on motivational representation (decreased left ventral-emotional processing-and right dorsal AI activity-salience processing) during both appetitive approach & aversive avoidance,	approach-avoidance (AA) motivational processes	76 healthy male students	(Yao et al., 2018)
Aggression, childhood maltreatment were measured by self-reported questionnaire-Childhood Trauma Questionnaire; Buccal cells -genotyping;		rs237885 rs4564970 rs1488467 rs468630	Intron 3-predicted affect transcript-tion 5'-UTR Upstream Most common SNPs associated with aggression	Ss with OXTR rs237885 TT genotypes >> risk of aggression compared to those who carried GG or GT genotypes under the recessive model; rs237885 a synergic additive interaction with childhood physical abuse on the aggression risk	Aggression	996 participants including 488 cases and 488 controls	(Zhang et al., 2018)

Used HEK-293T cells and sea urchin homogenates All in vitro experiments with cells or homogenates				CZ-48, a cell-permeant mimetic of NMN, activated SARM1 in vitro and in cellulo to cyclize NAD and produce a Ca2+ messenger, cADPR, with similar efficiency as NMN; SARM1 catalysis was similar to CD38, despite having no sequence similarity.			(Zhao et al., 2019)
Whole brain seed-based functional connectivity analyses for the basolateral, centromedial and superficial amygdala;	Amygdala; basolateral; centromedial; superficial; resting-state; functional connectivity; rs2268498; OXTR.	rs2268498.	upstream_transcript_variant associated with affiliative and social approach behavior.	stronger resting-state connectivity of all amygdala subregions to the fusiform and inferior occipital gyrus in TT- carriers compared to C-allele carriers. Additional modulations were found for the centromedial amygdala which showed stronger resting-state connectivity to inferior frontal regions and the insula in C-allele carriers and to brainstem regions in TT-carriers	subregional amygdala resting-state connectivity	N = 143 healthy participants (n = 52 males)	(Zimmermann et al., 2018)
QUESTIONNAIRES MINI LSAS	Plasma; OXT; Social Anxiety.	Extracted RIA assay		High plasma OXT with total LSAS score and FEAR subscale in SAD group	Social anxiety	N=23 SAD M N=28 M Controls	(Oh et al., 2018)
MOUSE: dyadic	Nanoparticles X BBB		Nano particles	>>Prosocial effects; [OXT]	Social behavior		(Oppong-Damoah et al., 2019)

social interactions familiar mice				>>CSF;>>brain; Acute – 3 days			
Pupil diameter; Amygdala activation from emotional stimuli			8 & 24 IU; novel Breath Powered nasal device, intravenous (IV) oxytocin, and placebo	Postdoc tests revealed reduced pupil diameter **solely after 8 IU** intranasal oxytocin; also significant relationship pupil diameter and right amygdala activation to faces & shapes		57 M	(Quintana et al., 2019b)
Saliva & plasma OXT levels **Concludes** in OXT does not reflect plasma levels but never measured plasma levels inference	Oxytocin; Endocrinology; Saliva; Neuropeptides; Plasma.		saliva oxytocin concentrations after 8 IU and 24 IU intranasal oxytocin are markedly inflated compared to saliva oxytocin concentrations after IV oxytocin and placebo	Two doses of Exhalation Delivery System delivered intranasal oxytocin (8 IU and 24 IU), intravenous oxytocin (1 IU) and placebo;		57 M	(Quintana et al., 2018)
Robust nano liquid chromatography-mass spectrometry (**nanoLC-MS**) platform for measuring the total amount of OXT in human				(R/A + robust nanoLC-MS) used to determine total OXT plasma/serum levels to startlingly high concentrations (high pg/mL-ng/mL**--~700 pg/ml**). Similar results were	Plasma OXT		(Brandtzaeg et al., 2016)

plasma/serum				obtained when combining R/A and ELISA; Compared to measuring free OXT, measuring total OXT can have advantages in e.g. biomarker studies.			

CH3 = methylation; SS social salience; < less than, lower than; >greater than, higher than; decreased/increased; [OXT] = oxytocin levels concentrations; Ss = subjects; F = female; M = male; Corr. = correlation; PL = placebo; WT = wildtype